

Omega-3 fatty acids supplementation on major cardiovascular outcomes: an umbrella review of meta-analyses of observational studies and randomized controlled trials

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Abstract. – OBJECTIVE: Omega-3 fatty acids are commonly used as a lipid-lowering agent or dietary supplement for the purpose of prevention of cardiovascular diseases. However, even large-scale clinical trials have not shown significant results demonstrating clear clinical benefits in cardiovascular diseases. Thus, this umbrella review aims to summarize and evaluate the evidence of clinical effects of omega-3 fatty acids supplementation on cardiovascular outcomes through comprehensive analyses of pre-

vious randomized controlled trials (RCTs) or observational cohort studies.

MATERIALS AND METHODS: We conducted relevant publication search in PubMed, Embase, and Cochrane Database of Systematic Reviews. We retrieved and analyzed 3,298 articles published until August 28th, 2019.

RESULTS: We identified 29 relevant articles and analyzed 83 meta-analyses of RCTs or cohort studies therefrom. As a result, we identified 12 cardiovascular outcomes that are related to

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omega-3 fatty acids supplementation. Among them, total mortality from major cardiovascular causes (RR 0.92, 95% CI 0.86 to 0.98) had significant inverse associations, and moreover, statistical significances were maintained even in subgroup analysis of large scale RCTs including more than 1,000 patients (RR 0.94, 95% CI 0.88 to 0.99).

CONCLUSIONS: Our umbrella review study shows that omega-3 fatty acids supplementation have a clinical benefit in reducing mortality from cardiovascular causes. However, many studies still have shown conflicting results, and therefore, further studies will be needed to verify the clinical benefit of omega-3 supplementation.

Key Words:

Omega-3 fatty acids, Cardiovascular outcome, Mortality, Meta-analysis, Systematic review.

Introduction

In the general population and among health-care professionals, it is widely recognized that omega-3 fatty acids exhibit properties that can potentially prevent cardiovascular diseases¹. However, controversy still exists due to discrepancies between available evidences². Significant results in clinical trials and observational studies of small patient groups have been reported³⁻⁵, but the true association remains unclear, as large clinical trials have often reported non-significant results⁶⁻⁸. Furthermore, the recently published Vitamin D and Omega-3 (VITAL) trial, a large-sized randomized controlled trial (RCT) that recruited 25,871 patients, concluded that marine omega-3 fatty acids supplementation has no effects in preventing cardiovascular diseases⁹.

Therefore, although systematic reviews and meta-analyses have attempted to synthesize the results from numerous clinical trials and observational studies investigating the effect of omega-3 supplementation on cardiovascular outcomes, they reached no definite conclusion. Several recent systematic reviews have performed quantitative syntheses of the vast amount of available evidences. Among them, a recent systemic review indicated the beneficial effect of omega-3 supplementation on cardiovascular diseases¹⁰, while the other review showed the positive effect of omega-3 fatty acids but only a small effect with moderate- and low-certainty evidence¹¹.

The aim of this umbrella review was, therefore, to examine the effect of omega-3 fatty acids supplementation on cardiovascular diseases avoid-

ing research biases, and thereby overcoming the shortcomings of previous studies.

Materials and Methods

We performed an umbrella review assessing the effects of omega-fatty acids supplementation on cardiovascular outcomes according to a pre-registered protocol in PROSPERO (registration number: CRD42018115797). We reported the results according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA)¹².

Literature Search Strategy and Eligibility Criteria

We searched PubMed, Embase, and Cochrane Database of Systematic Reviews (CDSR) from their inception to August 28th, 2019 to identify meta-analyses that investigated the association between omega-3 supplementation and cardiovascular outcomes. We performed a publication search using the following keywords: omega-3 fatty acids, n-3 fatty acids, w-3 fatty acids, α -linolenic acid, ALA, eicosapentaenoic acid, EPA, docosahexaenoic acid, DHA, polyunsaturated fatty acids, PUFA, long chain polyunsaturated fatty acids, LCPUFA, fish oil, and meta.

Only English articles were eligible. We first screened titles, followed by the abstract, and then the full text of potentially eligible articles. We only included systematic reviews containing meta-analyses that investigated the effect of omega-3 fatty acids supplementation on cardiovascular disease. On the other hand, we did not include studies on the relationship between fish consumption and cardiovascular outcome, because fish contains various nutrients other than omega-3 fatty acids. For example, a RCT that examined the difference in effects of between fresh fish consumption and omega-3 fatty acids supplementation concluded that fish consumption was associated with positive cardiovascular outcomes, but omega-3 fatty acids supplementation was not¹³. In addition, we excluded meta-analyses that studied dietary interventions such as Mediterranean diet education and food frequency questionnaire results.

Inclusion of meta-analysis was independent of the study design of the component study (i.e. either RCTs or observational studies). There was no restriction of the study population. If an article included more than one eligible meta-analysis, we included these separately.

Data Extraction

From each eligible article, we extracted the name of the first author and the date of publication. From each eligible meta-analysis, we extracted the outcome of interest, the number of cardiovascular outcome events and total participants, individual study estimates and corresponding 95% confidence interval (CI), metrics used for analyses such as odds ratio (OR), risk ratio (RR), and hazard ratio (HR), and individual study designs as RCT or observational study. We also extracted the summary effect estimates and meta-analysis model of the original meta-analyses to check whether the original results were consistent with the results of our re-analysis. From the meta-analyses of observational studies, we extracted the maximally adjusted study estimate available.

Statistical Analysis

We estimated the summary effects, corresponding 95% CIs and p -values using both fixed- and random-effects models¹⁴. We also estimated between-study heterogeneity as the I^2 metric^{15,16}. I^2 statistic above 50% and 75% are usually judged to represent large and very large heterogeneity, respectively¹⁷. To assess the reliability of analyses, we adopted a series of statistical tests and bias assessment methods. We estimated the 95% prediction interval, which is the range for the true effect of the intervention for 95% of similar studies in the future¹⁸. In addition, we assessed the small study effect with the regression asymmetry test proposed by Egger et al¹⁹ because small studies may overestimate the effect size. We claimed a small study effect with a p -value < 0.1 . Presence of small study effects indicates reporting bias such as publication bias, poor methodological quality of individual studies, or genuine heterogeneity²⁰. We also defined the study with the smallest standard error as the largest study, and assumed that the largest study reflects the true effect size. The expected number of significant studies was obtained by multiplying the power of the largest study with the number of all studies in the meta-analysis²¹. We assessed the presence of excess significance bias which was determined if the observed number of studies reporting nominally statistically significant result were greater than the expected number of studies reporting a significant result^{22,23}.

For meta-analyses of RCTs, we performed subgroup analyses according to the total number of participants (above 1,000 or below 1,000) and compared their results. For outcomes presented in

both meta-analyses of RCTs and meta-analysis of observational studies, we compared the summary effects of the two study designs.

In addition, we applied credibility ceilings to the meta-analyses of observational studies. We assumed that due to inherent methods used in observational studies, any observational study could not give more than 100-c% (c = credibility ceiling) probability of an effect being in a particular direction and not in the other^{24,25}. We obtained the I^2 index and the random-effects summary estimate of meta-analyses of observational studies under various credibility ceilings ranging from 5% to 20%.

All statistical tests and reported p -values are two-sided. The software used for analysis was Comprehensive Meta-analysis ver.3.3.070 (Borenstein, NH, USA), R Studio ver. 1.1.456., and R package “metafor” and “pwr”²⁶⁻²⁸.

Results

Selection of Eligible Meta-Analyses

We identified 1,771 articles from a PubMed, 1,977 articles from a Embase, and 349 articles from a CDSR search (Figure 1). We excluded 799 duplicate articles. From 3,298 unique articles reviewed by title screening, we excluded 1,460 articles not related to omega-3 fatty acids supplementation. From 1,838 articles reviewed by abstract screening, we excluded 1,385 articles, of which 126 articles were conference abstracts, 399 articles did not contain respective interventions, 71 articles did not contain meta-analyses, and 789 articles did not contain cardiovascular outcomes. After the full-text screening of 453 articles, 29 articles were finally judged to be eligible for inclusion in our analysis.

From the 29 eligible articles, 83 eligible meta-analyses were identified, from which data were extracted. From 76 meta-analyses of RCTs, 31 (41%) were statistically significant ($p < 0.05$). Nine-teen (25%) had large heterogeneity ($50\% < I^2 < 75\%$) and 1 (1%) had very large heterogeneity ($I^2 > 75\%$). Seventeen (22%) had significant bias of small study effect. Eight (11%) had prediction intervals excluding the null. Of 7 meta-analyses of observational cohort studies, 4 (57%) were statistically significant ($p < 0.05$). One (14%) had large heterogeneity ($50\% < I^2 < 75\%$) and 2 (29%) had very large heterogeneity ($I^2 > 75\%$). One (14%) had significant bias of small study effect. All 7 (100%) lost significance under 10% credibility

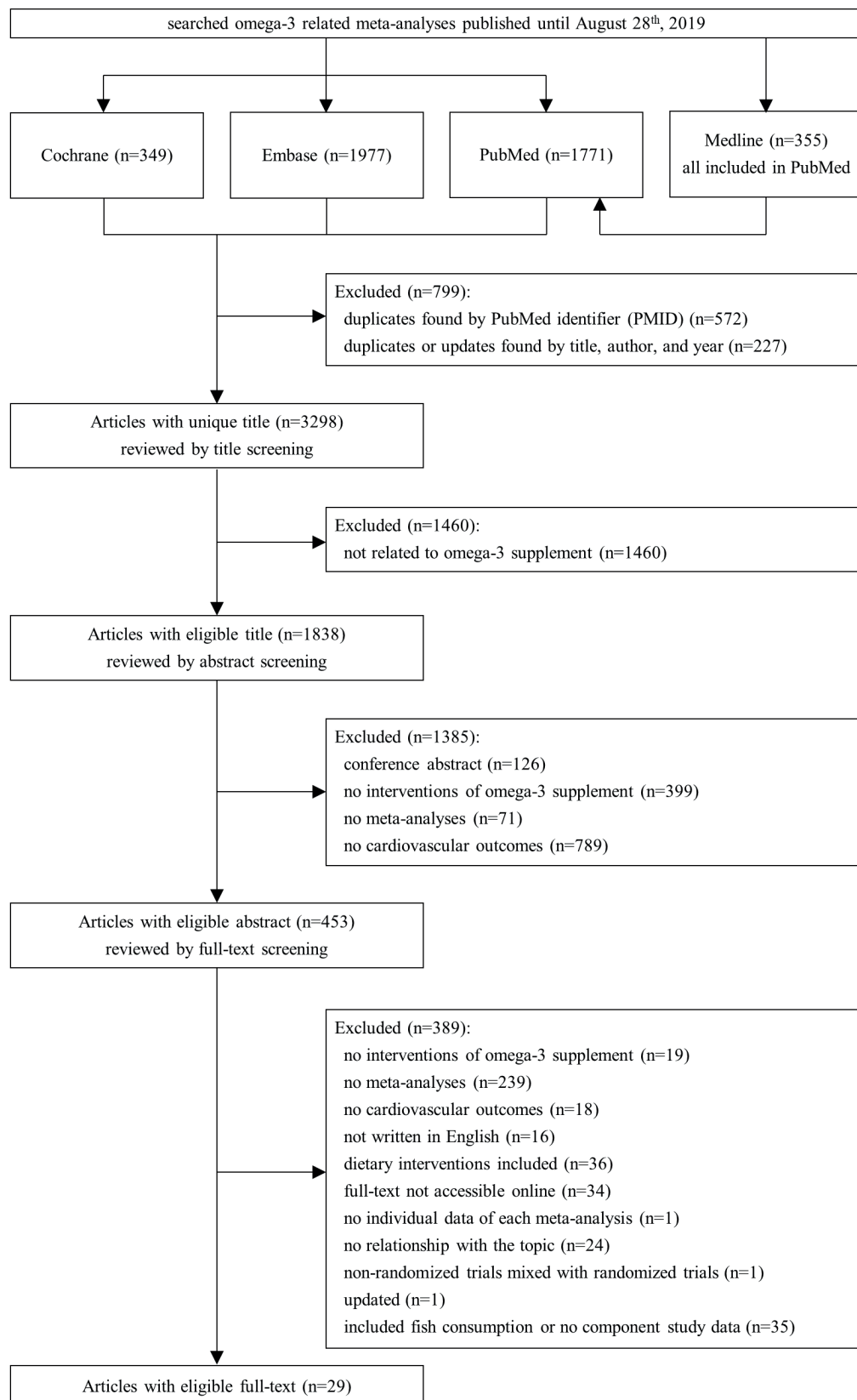


Figure 1. Flow chart of literature search.

ceiling. One (14%) had prediction interval excluding the null.

Determination of Cardiovascular Outcomes

We identified 11 cardiovascular outcomes from the literatures, which included cardiovascular, cardiac, and coronary events, cardiovascular, cardiac, and coronary deaths, arrhythmia or sudden death, myocardial infarction, stroke or transient ischemic attack, post-operative atrial fibrillation, and recurrent atrial fibrillation. Although these outcomes were similar to each other, we followed the definition and terminology of the eligible articles as they were. In addition, we created a composite outcome, total mortality from major cardiovascular causes by merging component studies reporting any of the following: cardiovascular, cardiac, coronary, or sudden deaths. Eventually, we were able to analyze 12 outcomes in the meta-analyses of RCTs and 6 outcomes in observational cohort studies.

Total Mortality from Major Cardiovascular Causes in Meta-Analyses of RCTs

Meta-analyses from 5 articles were merged for total mortality from major cardiovascular causes. In total, 26 RCTs including 82,696 participants having more than 3,250 ($> 3.9\%$) events were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.92, 95% CI 0.86 to 0.98, $p = 0.014$) in reducing overall mortality of major cardiovascular causes. There was a low heterogeneity between component studies ($I^2 = 4\%$), and small study effect bias was observed. The 95% prediction interval did not exclude the null (0.83 to 1.02) (Table I). There was no excess significance bias.

Cardiovascular Death in Meta-Analyses of RCTs

Meta-analyses from 3 articles were merged for cardiovascular death. In total, 22 RCTs including 76,407 participants with more than 3,192 ($> 4.2\%$) events were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.93, 95% CI 0.88 to 0.98, $p = 0.012$). There was low heterogeneity between component studies ($I^2 = 0\%$). There was small study effect bias. The 95% prediction interval did not exclude the null (0.87 to 0.99) (Table I). There was no excess significance bias.

Cardiac Death in Meta-Analyses of RCTs

Three articles derived from meta-analyses were merged for cardiac death. In total, 20 RCTs with

more than 79,410 participants reported 3,618 (4.6%) events. The effect of omega-3 fatty acids supplementation was statistically significant (RR 0.90, 95% CI 0.82 to 1.00, $p = 0.040$). Low heterogeneity between component studies ($I^2 = 20\%$) was found in our analysis. There was small study effect bias. The 95% prediction interval did not exclude the null (0.74 to 1.10) (Table I). There was no excess significance bias.

Post-operative Atrial Fibrillation in Meta-Analyses of RCTs

Meta-analyses from 3 articles were merged for post-operative atrial fibrillation. In total, 21 RCTs with 4,201 participants were included, and a total of 1,247 (29.7%) events were recorded. The overall effect of omega-3 fatty acids supplementation was statistically significant (OR 0.65, 95% CI 0.51 to 0.82, $p < 0.001$). There was relatively large heterogeneity between component studies ($I^2 = 53\%$). There was small study effect bias. The 95% prediction interval did not exclude the null (0.29 to 1.45) (Table I). Excess significance bias was found.

Other Outcomes in Meta-Analyses of RCTs

Meta-analyses of the other 8 outcomes did not reveal significant associations, including cardiovascular events, cardiac events, coronary events, coronary deaths, arrhythmia or sudden deaths, myocardial infarction, stroke or transient ischemic attack, and recurrent atrial fibrillation (Table I). There was relatively large heterogeneity between component studies for recurrent atrial fibrillation ($I^2 = 74\%$), and not for the other 7 outcomes.

Total Mortality from Major Cardiovascular Causes in Meta-analyses of Cohort Studies

There was only one article reporting total mortality from major cardiovascular causes. A total of 558,826 participants derived from 15 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.76, 95% CI 0.65 to 0.90, $p = 0.0013$). There was relatively large heterogeneity between component studies ($I^2 = 60\%$). There was no small study effect bias. The 95% prediction interval did not exclude the null (0.45 to 1.28) (Table II). A loss of significance under 10% credibility ceiling was found.

Coronary Events in Meta-Analyses of Cohort Studies

Again, only one article was reported for coronary events. A total of 344,722 participants from

Table I. Meta-analyses of randomized controlled trials of omega-3 fatty acids on major cardiovascular outcomes.

Cardiovascular outcome	Population	Events/total participants	Number of study estimates	Effect metrics	Random effects summary estimate (95% CI)	Random effects <i>p</i> value	I ² (%)	95% prediction interval	Evaluation of biases*
Total mortality of major cardiovascular cause ³⁵⁻³⁹	Overall	>3,250 / 82,696	26	RR	0.92 (0.86 to 0.98)	0.014	4	0.83 to 1.02	Small study effects
Cardiovascular event ⁴¹⁻⁴⁵	Overall	17,033 / >72,179	39	RR	0.97 (0.92 to 1.03)	0.330	45	0.80 to 1.18	None
Cardiac event ⁴⁶	With coronary heart disease	2,852 / 25,134	10	OR	0.92 (0.79 to 1.06)	0.250	49	0.63 to 1.33	None
Coronary event ⁴⁵	Overall	6,093 / 77,917	10	RR	0.95 (0.89 to 1.03)	0.210	0	0.88 to 1.04	None
Cardiovascular death ^{35,38,39}	Overall	>3,192 / 76,407	22	RR	0.93 (0.88 to 0.98)	0.012	0	0.87 to 0.99	Small study effects
Cardiac death ^{36,37,47}	Overall	3,618 / 79,410	20	RR	0.90 (0.82 to 1.00)	0.040	20	0.74 to 1.10	Small study effects
Coronary death ⁴⁵	Overall	2,695 / 77,917	10	RR	0.93 (0.84 to 1.03)	0.150	0	0.82 to 1.05	None
Arrhythmia or sudden death ^{46,48,49}	Overall	1,415 / 43,987	12	OR	0.85 (0.71 to 1.02)	0.086	32	0.57 to 1.28	None
Myocardial infarction ^{38,45,47}	Overall	2,846 / 86,411	20	RR	0.90 (0.80 to 1.00)	0.056	13	0.72 to 1.12	None
Stroke or transient ischemic attack ^{41,47}	Overall	259 / 32,026	11	RR	1.20 (0.94 to 1.53)	0.150	0	0.90 to 1.59	None
Post-operative atrial fibrillation ⁵⁰⁻⁵²	Underwent cardiac surgery	1,247 / 4,201	21	OR	0.65 (0.51 to 0.82)	< 0.001	53	0.29 to 1.45	Large heterogeneity; small study effects; excess significance bias
Recurrent atrial fibrillation ⁵³	With previous atrial fibrillation	894 / 1,990	8	OR	0.81 (0.52 to 1.25)	0.340	74	0.21 to 3.14	Large heterogeneity

All statistical tests are two-sided. **Bold** Summary effect was statistically significant. *Presence of large heterogeneity, small study effects, or excess significance bias. **Abbreviations:** CI, confidence interval; NR, not reported; OR, odds ratio; RR, risk ratio.

14 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.89, 95% CI 0.84 to 0.96, $p = 0.001$). A low heterogeneity between component studies ($I^2 = 3\%$) was found. There was no small study effect bias. The 95% prediction interval excluded the null (0.82 to 0.98) (Table II). There was a loss of significance under 10% credibility ceiling.

Coronary Deaths in Meta-Analyses of Cohort Studies

There was only one article reporting coronary deaths. A total of 357,621 participants from 10 cohorts was included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.85, 95% CI 0.73 to 1.00, $p = 0.047$). There was no large heterogeneity between component studies ($I^2 = 49\%$), nor small study effect bias. The 95% prediction interval did not exclude the null (0.57 to 1.29) (Table II). There was a loss of significance under 10% credibility ceiling.

Arrhythmia or Sudden Deaths in Meta-Analyses of Cohort Studies

There was only one article reporting on arrhythmia or sudden deaths. In total, 201,205 participants of 5 cohorts were included. The overall effect of omega-3 fatty acids supplementation was statistically significant (RR 0.53, 95% CI 0.41 to 0.67, $p < 0.001$). There was no heterogeneity between component studies ($I^2 = 0\%$). There was no small study effect bias. The 95% prediction interval excluded the null (0.36 to 0.78) (Table II). A loss of significance under 10% credibility ceiling was found.

Other Outcomes in Meta-Analyses of Cohort Studies

Both other outcomes, cardiovascular events and myocardial infarction, were not statistically significant (Table II). There was very large heterogeneity between component studies of cardiovascular events ($I^2 = 77\%$), and relatively large heterogeneity between component studies of myocardial infarction ($I^2 = 72\%$).

Comparison of Meta-Analyses Between RCTs and Cohort Studies

Twelve outcomes have been reviewed from the meta-analyses of RCTs, and 6 outcomes have been reviewed from the meta-analyses of cohort studies. From the 6 overlapping outcomes, only 1 outcome of a meta-analysis of RCTs and 4 out-

comes of meta-analyses of cohort studies showed statistical significance ($p < 0.05$ for random-effect model) (Table III). For the outcome of total mortality of major cardiovascular causes, the meta-analysis of RCTs and cohort studies both showed statistical significance. For the outcomes of coronary events, coronary deaths, and arrhythmia or sudden deaths, only meta-analyses of cohort studies showed statistical significance while meta-analyses of RCTs did not. For the outcomes of cardiovascular event and myocardial infarction, both meta-analyses of RCTs and cohort studies did not show statistical significance (Figure 2).

Comparison of Meta-Analyses Between RCTs with More Than 1,000 Participants and Less Than 1,000 Participants

While the effect sizes reported from the largest cohort studies were similar compared to the meta-analyses of cohort studies, the discrepancy was present between the effect size reported from the largest RCTs and the meta-analyses of RCTs, which underlines the need for subgroup analysis according to the number of total participants ($> 1,000$ vs. $< 1,000$) (Table III and Figure 2).

Out of all 12 major cardiovascular outcomes, total mortality from major cardiovascular causes, cardiovascular death, cardiac death, and postoperative atrial fibrillation showed statistical significance in meta-analyses of RCTs with less than 1,000 participants, whereas only 2 outcomes were still supported by statistical significance even in meta-analyses of RCTs of total participants larger than 1,000. These 2 outcomes were total mortality from major cardiovascular causes (RR = 0.94, 95% CI 0.88 to 0.99) and cardiovascular deaths (RR = 0.94, 95% CI 0.89 to 1.00) (Table III).

Notably, there was a tendency for the meta-analyses of RCTs with less than 1,000 participants to report a dramatically larger effect size (RR = 0.58 for total mortality of major cardiovascular causes, RR = 0.61 for cardiovascular death, RR = 0.60 for cardiac death) compared to those with more than 1,000 participants (RR = 0.94 for total mortality from major cardiovascular causes, RR = 0.94 for cardiovascular death, RR = 0.93 for cardiac death) (Table III). These 2 outcomes had small study effects as well.

Nonetheless, when subgroup analysis was conducted with RCTs of more than 1,000 patients, statistical significance for total mortality from major cardiovascular causes was maintained ($p = 0.033$) with low heterogeneity ($I^2 = 0\%$), and there was no small study effect. As for cardio-

Table II. Meta-analyses of cohort studies of omega-3 fatty acids on major cardiovascular outcomes.

Cardiovascular outcome	Population	Events/total population	Number of study estimates	Effect metrics	Random effects summary estimate (95% CI)	Random effects <i>p</i> value	I ² (%)	95% prediction interval	Evaluation of biases *
Total mortality from major cardiovascular causes⁵⁴	Non-hospitalized adults of at least 18 years old	NR/558,826	15	RR	0.76 (0.65 to 0.90)	< 0.001	60	0.45 to 1.28	Large heterogeneity
Cardiovascular event ⁴¹	Overall	1842/68,954	6	RR	0.97 (0.78 to 1.21)	0.800	77	0.49 to 1.94	Large heterogeneity
Coronary event⁵⁵	Overall	NR/344,722	14	RR	0.89 (0.84 to 0.96)	0.001	3	0.82 to 0.98	Loss of significance under 10% credibility ceiling
Coronary death⁵⁴	Non-hospitalized adults of at least 18 years old	NR/357,621	10	RR	0.85 (0.73 to 1.00)	0.047	49	0.57 to 1.29	Loss of significance under 10% credibility ceiling
Arrhythmia or sudden death⁵⁴	Non-hospitalized adults of at least 18 years old	NR / 201,205	5	RR	0.53 (0.41 to 0.67)	< 0.001	0	0.36 to 0.78	Loss of significance under 10% credibility ceiling
Myocardial infarction ⁵⁴	Non-hospitalized adults of at least 18 years old	NR/274,083	7	RR	0.91 (0.74 to 1.11)	0.340	72	0.48 to 1.70	Large heterogeneity

All statistical tests are two-sided. **Bold** Summary effect was statistically significant. *Large heterogeneity, small study effects, excess significance bias, or loss of heterogeneity under 10% credibility ceiling. **Abbreviations:** CI, confidence interval; NR, not reported; OR, odds ratio; RR, risk ratio.

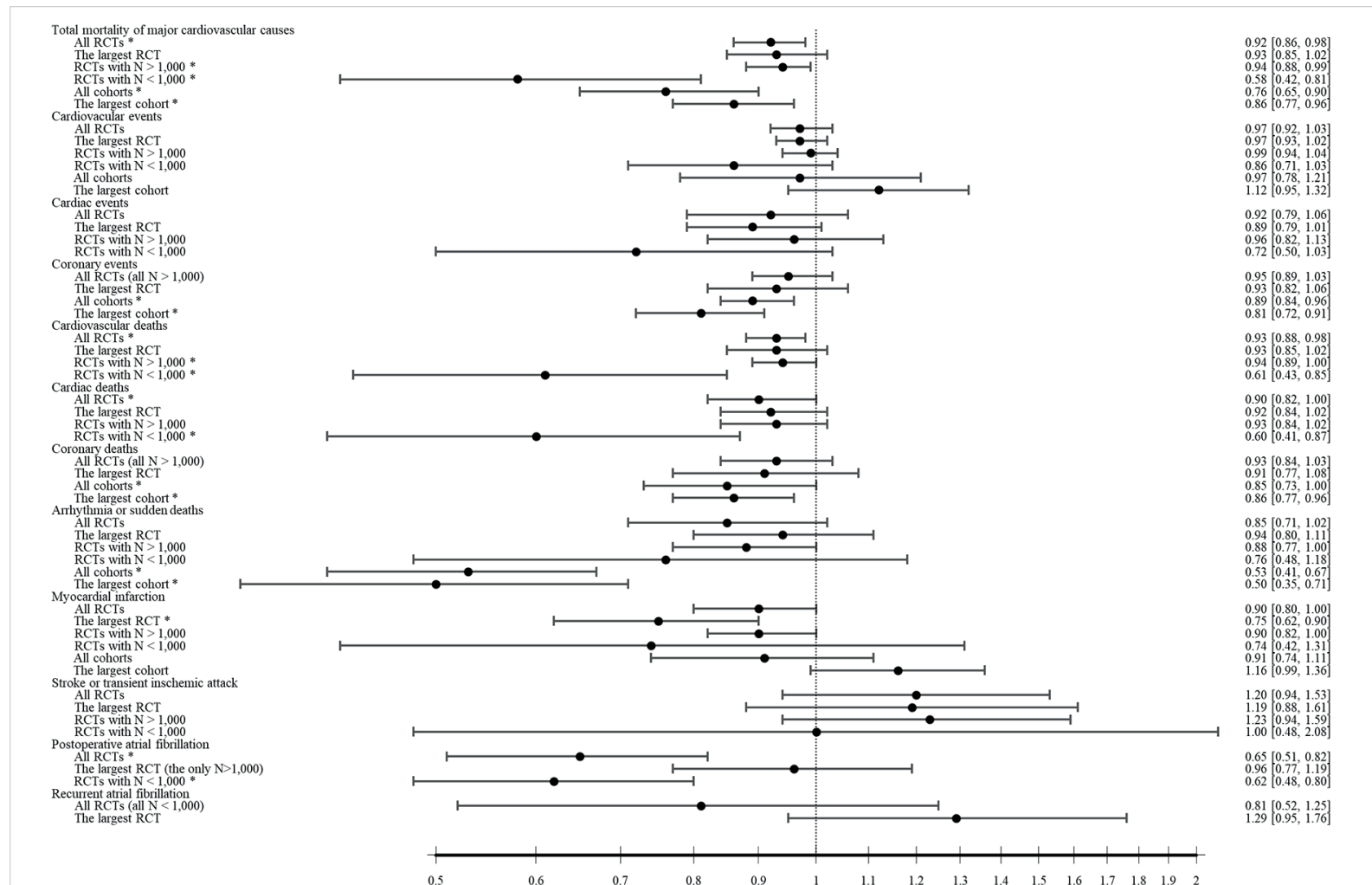


Figure 2. Forest plot of meta-analyses of randomized controlled trials and cohort studies for all the categories of major cardiovascular outcomes.

Table III. Comparison and Subgroup analyses of randomized controlled trials and cohort studies.

	Randomized controlled trials					Cohort studies		
Cardiovascular outcome	Metric	Meta-analysis of RCTs	The largest RCT	Meta-analysis of RCTs with participants > 1,000	Meta-analysis of RCTs with participants < 1,000	Metric	Meta-analysis of cohort studies	The largest cohort study
Total mortality from major cardiovascular causes	RR	0.92 (0.86 to 0.98)*	0.93 (0.85 to 1.02)	0.94 (0.88 to 0.99)*	0.58 (0.42 to 0.81)*	RR	0.76 (0.65 to 0.90)*	0.86 (0.77 to 0.96)*
Cardiovascular event	RR	0.97 (0.92 to 1.03)	0.97 (0.93 to 1.02)	0.99 (0.94 to 1.04)	0.86 (0.71 to 1.03)	RR	0.97 (0.78 to 1.21)	1.12 (0.95 to 1.32)
Cardiac event	OR	0.92 (0.79 to 1.06)	0.89 (0.79 to 1.01)	0.96 (0.82 to 1.13)	0.72 (0.50 to 1.03)	NA	NA	NA
Coronary event	RR	0.95 (0.89 to 1.03)	0.93 (0.82 to 1.06)	0.95 (0.89 to 1.03)	NA	RR	0.89 (0.84 to 0.96)*	0.81 (0.72 to 0.91)*
Cardiovascular death	RR	0.93 (0.88 to 0.98)*	0.93 (0.85 to 1.02)	0.94 (0.89 to 1.00)*	0.61 (0.43 to 0.85)*	NA	NA	NA
Cardiac death	RR	0.90 (0.82 to 1.00)	0.92 (0.84 to 1.02)	0.93 (0.84 to 1.02)	0.60 (0.41 to 0.87)*	NA	NA	NA
Coronary death	RR	0.93 (0.84 to 1.03)	0.91 (0.77 to 1.08)	0.93 (0.84 to 1.03)	NA	RR	0.85 (0.73 to 1.00)*	0.86 (0.77 to 0.96)*
Arrhythmia or sudden death	OR	0.85 (0.71 to 1.02)	0.94 (0.80 to 1.11)	0.88 (0.77 to 1.00)	0.76 (0.48 to 1.18)	RR	0.53 (0.41 to 0.67)*	0.50 (0.35 to 0.71)*
Myocardial infarction	RR	0.90 (0.80 to 1.00)*	0.75 (0.62 to 0.90)*	0.90 (0.82 to 1.00)	0.74 (0.42 to 1.31)	RR	0.91 (0.74 to 1.11)	1.16 (0.99 to 1.36)
Stroke or transient ischemic attack	RR	1.20 (0.94 to 1.53)	1.19 (0.88 to 1.61)	1.23 (0.94 to 1.59)	1.00 (0.48 to 2.08)	NA	NA	NA
Postoperative atrial fibrillation	OR	0.65 (0.51 to 0.82)*	0.96 (0.77 to 1.19)	NA	0.62 (0.48 to 0.80)*	NA	NA	NA
Recurrent atrial fibrillation	OR	0.81 (0.52 to 1.25)	1.29 (0.95 to 1.76)	NA	0.81 (0.52 to 1.25)	NA	NA	NA

All statistical tests are two-sided. Underline means overlapping outcomes. *Summary effect was statistically significant ($p < 0.05$). Abbreviations: NA, not available; OR, odds ratio; RCT, randomized controlled trial; RR, risk ratio.

vascular deaths, statistical significance was also maintained ($p = 0.043$) with low heterogeneity ($I^2 = 0\%$), and there was no small study effect.

Discussion

Even though a clear clinical benefit has not been established, it has been assumed that omega-3 fatty acids supplementation might have some beneficial effect on cardiovascular outcomes²⁹. However, previous large clinical trials demonstrated no evidence of the effect of omega-3 fatty acids supplementation on various cardiovascular outcomes. The OMEGA trial, a randomized, placebo-controlled, double-blind, multicenter trial included 3,851 participants with one year of follow-up and concluded that omega-3 fatty acids supplementation did not reduce sudden cardiac deaths and cardiovascular events⁶. The ORIGIN trial concluded that omega-3 fatty acids supplementation did not reduce cardiovascular events in patients with dysglycemia⁷. The Risk and Prevention Study trial concluded that omega-3 fatty acids supplementation did not reduce cardiovascular mortality⁸. Even the VITAL trial, the most recently conducted clinical trial of omega-3 fatty acids, showed that omega-3 fatty acids supplementation did not reduce the incidence of major cardiovascular events⁹.

There have been 3 umbrella reviews comparing the effects of various nutrients including omega-3 and cardiovascular outcome to date³⁰⁻³², but to the best of our knowledge, an umbrella review focusing only omega-3 effects on cardiovascular outcomes has not been conducted. In particular, in this current review study, we aimed to identify true associations between omega-3 fatty acids and cardiovascular outcome more strictly by excluding biases and performing subgroup analyses. Furthermore, we comprehensively analyzed previous literature by including RCTs as well as observational cohort studies.

In our study, total mortality from major cardiovascular causes showed statistical significance from meta-analyses of cohort studies despite large heterogeneity. In addition, the meta-analyses of RCTs also showed that total mortality from major cardiovascular causes was reduced by omega-3 fatty acids supplementation with statistical significance. Furthermore, when we performed subgroup-analyses to verify the reliability of evidence more strictly, statistical significance was maintained even in the case of RCTs with more

than 1,000 participants. From the meta-analyses of RCTs with more than 1,000 participants, the bias of small study effects was not detected, showing that the significant effects were persistent among the large-sized RCTs without any significant bias that had to be considered during the review.

Interestingly, in our umbrella review, most cardiovascular outcomes other than mortality did not show significant associations with omega-3 fatty acids supplementation. Rather, only mortality from cardiovascular causes had an inverse relationship with omega-3 fatty acids supplementation. The result is somewhat intriguing because mortality was reduced by omega-3 fatty acids supplementation, while less severe cardiac events were not affected. Although we are not sure of the exact reason for such a paradoxical result, we can consider the possibility that it may be due to the differences in clarity of clinical presentation and probability of diagnosis of each outcome. For example, severe diseases such as myocardial infarction are usually well-diagnosed with clear clinical manifestations, whereas less severe diseases such as ischemic heart disease and transient ischemic attack often have sub-clinical presentation and may not have been properly diagnosed due to silent symptoms. On the other hand, death is an uncontroversial clinical outcome and the diagnosis is definitive. In this case, mortality may be a more reliable outcome and may reflect more accurately the clinical effect of a medical intervention. We believe that our study may have had paradoxical results for this same reason, and that the significant reduction in mortality by omega-3 supplementation is reliable even in the absence of clinical significance for other relevant outcomes.

Strengths and Limitations

This umbrella review is distinct from the prior umbrella review, since we examined the effect of only omega-3 fatty acids on various cardiovascular outcomes of specific causes. A recent comprehensive meta-analysis¹¹ studied the effect of omega-3 fatty acids on cardiovascular outcomes, which included individual studies assessing dietary interventions such as advising to increase oily fish consumption, while we focused on the effects of omega-3 fatty acids supplement only. The meta-analysis¹¹ concluded that alpha-linolenic acid, a type of omega-3 fatty acids, reduces coronary heart disease mortality, prevalence of arrhythmia, and cardiovascular disease events. However, this might not necessarily mean that these beneficial effects are the results of omega-3

fatty acids intake, because fish intake is nutritionally different from omega-3 fatty acids intake alone. There is evidence from a RCT¹² that fish intake of 500g per week has beneficial effects on cardiovascular outcomes, while omega-3 fatty acids supplementation dose not. Indeed, during the literature research, we identified several articles^{33,34} which concluded that omega-3 fatty acids intake was beneficial in preventing cardiovascular disease but included component studies of dietary interventions in their meta-analyses, which may not act as sufficient evidence for the effect of the omega-3 fatty acids alone on cardiovascular outcome.

This umbrella review has advantages over previous meta-analyses because it includes quantitative analyses of all non-overlapping component studies derived from meta-analyses showing different conclusions. Several previous articles concluded that omega-3 fatty acids supplementation has a beneficial effect on cardiovascular outcomes, based on the statistically significant results of their meta-analyses. Among the eligible meta-analyses in our review, evidence of RCTs studying the association with omega-3 fatty acids supplementation and total mortality from major cardiovascular events were studied by a total of five articles, with two of them concluding significant associations^{35,36} and three of them concluding non-significant associations³⁷⁻³⁹. Our meta-analysis included all non-overlapping component studies from the meta-analyses of these 5 articles and showed that the association was statistically significant, even when the analysis was restricted to RCTs with more than 1,000 patients. In addition, the association of omega-3 fatty acids supplementation and cardiovascular events was studied by a total of 6 articles. One of these studies concluded a statistically significant association⁴⁰, while 5 of them found non-significant associations⁴¹⁻⁴⁵. In our meta-analysis that included all non-overlapping component studies from the meta-analyses of these 6 articles, we found that the association was not statistically significant, implying that there was no significant positive effect of omega-3 fatty acids supplementation on the overall number of cardiovascular events.

There are several limitations which need to be taken into account. First, we systematically searched and identified results of meta-analyses, which means that recent clinical trials might have been overlooked. However, for the outcomes of total mortality of cardiac causes, cardiovascular events, coronary events, cardiovascular deaths, coronary deaths, and myocardial infarctions, we

identified and included meta-analyses published in 2018, so it is likely that this review includes recent clinical trials for these outcomes. Additionally, we also have conducted meta-analyses including the latest trial⁹ reported on January 3rd, 2019. This RCT reported five major cardiovascular outcomes, total mortality from cardiovascular causes, cardiovascular events, cardiovascular deaths, myocardial infarctions, stroke or transient ischemic attack. The results of meta-analyses were not different from the previous meta-analyses we had. Second, we did not evaluate the quality of individual component studies, which is the responsibility of the authors of the original meta-analyses and was beyond the scope of our review. Third, because we did not list and consider the amount of fish consumption, we could not deny the possibility that the random effect of fish consumption could be greater and obscured the effect of omega-3 fatty acids, which could be a strong reason why various outcomes were not statistically significant.

Conclusions

Our umbrella review indicates that omega-3 fatty acids supplementation reduces overall mortality from cardiovascular causes. Even though a few large RCTs showed no evidence of clinical effect of omega-3 on cardiovascular outcomes, our comprehensive review study still provides a clue of clinical utility of omega-3 fatty acids supplementation. Considering that there have been conflicting results in many existing studies, in future clinical trials, it is necessary to identify the true clinical evidence concerning omega-3 fatty acids supplementation through efforts to reduce various research biases.

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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